

How Should We Conduct Studies on Interventions That Promote Clinically Relevant Increases in Physical Activity?

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In this issue of the *Revista Española de Cardiología*, García-Ortiz et al¹ provide pertinent data addressing the potential clinically relevant effects of a behavioral intervention to increase physical activity levels in a primary care setting, a frontline approach which if successfully implemented may impact large numbers of sedentary individuals. Physical inactivity represents an almost universal risk factor whose avoidance has benefits for coronary heart disease,² stroke,³ diabetes,⁴ hypertension,⁵ obesity,⁶ and other vascular outcomes. Therefore, all efforts to increase physical activity, particularly among sedentary individuals, remain a critical public health priority. Injuries due to participating in various forms of physical activity appear to be the only obvious—though opportunistic—downside. In addition, concerns about the impact of more vigorous forms of physical exertion on sudden cardiac death are valid,⁷ but the absolute rates of occurrence should minimize these concerns relative to the myriad benefits of physical activity.

Whereas the epidemiologic evidence has consistently demonstrated that higher levels of physical activity or fitness are associated with reductions in cardiovascular disease and other health outcomes,⁸ the shape of any such association remains an active area of debate.² Whether considering the total amount, specific types, or various intensities of physical activity, it is not a simple “more is better” mantra. Many observational

studies alternatively suggest L-shaped (no effect until a certain threshold of physical activity is attained) or J-shaped (greater benefits with greater physical activity, but then risk emerges at high levels) associations with cardiovascular disease. This may be particularly important when considering the relevance of various mechanisms, via coronary risk factors and biomarkers, through which increasing physical activity would help to prevent cardiovascular disease. Mechanistically, increases in physical activity simultaneously affect multiple organ systems; behaviorally, increasing physical activity corresponds with other lifestyle and dietary improvements.

So how do we interpret the results from this well-conducted, large-scale intervention trial by García-Ortiz et al¹ that garnered modest increases in physical activity levels, but no significant differences in risk factors and biomarkers when comparing the active versus control groups? In their defense, their physical activity intervention was not designed to reduce coronary risk factors per se, but given that the presence of established mechanisms through physical activity leads to reductions in cardiovascular disease risk, we expect some measurable effect to emerge. In fact, this study highlights four key factors in physical activity epidemiology and clinical trials that we need to more carefully consider as we embark on subsequent efforts to increase physical activity on either an individual or population-based level.

First, the selection of an appropriate target population to increase physical activity levels is critical. The author's selection of largely healthy middle-aged and older adults was appropriate, with the goal of encouraging long-term increases in physical activity over time. But what is more complicated is the identification and definition of truly sedentary, physically inactive individuals. More sedentary individuals are more likely to not only increase physical activity levels, but also to a greater magnitude and minimize any regression to the mean. For this study, the investigators identified

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subjects not meeting the American College of Sports Medicine/Centers for Disease Control (ACSM/CDC) physical activity guidelines of 30 minutes/day of moderate-intensity physical activity 5 days/week or 20 minutes/day of vigorous-intensity physical activity 3 days/week.⁹ However, the intervention and control subjects still expended an average of 34 minutes/week of either moderate- or vigorous intensity physical activity at baseline - somewhere between sedentary and physically active. While both the intervention and control groups increased physical activity levels, their baseline levels may have already been sufficiently high to mute any potential improvements in coronary risk factors and biomarkers, thus explaining the small benefits on blood pressure and HDL cholesterol (HDL-C) that were not different in magnitude between the intervention and control groups.

Second, we can safely assume corresponding changes or improvements in coronary risk factors, dietary factors, and biomarkers during the 12 month intervention period were similar in both the intervention groups as part of a randomized clinical trial. However, particularly in intervention trials involving behavioral modification, recidivism may have blunted the findings by 12 months. The main trial presented findings after 6 months follow-up,¹⁰ at which time there may have been greater differences comparing the intervention and control groups that became more similar by 12 months follow-up. Long-term adherence remains a challenge for physical activity interventions in the primary care setting.^{11,12} More direct, regular patient interaction by general practitioners, cardiologists, and other health care providers, as tested here, offers promise in promoting increases in physical activity and improvements in cardiovascular risk profiles.

Third, a priori power estimates for clinical trials are important for planning and funding purposes, but often get away from the broader clinical implications of achieving small, permanent increases in physical activity levels over time that are immune from poor long-term adherence. This is not to diminish the importance of planning intervention studies of physical activity with specific targets in mind, but rather to encourage researchers and clinicians alike to avoid using statistics as the sole arbiter of an intervention's success. Any increase in physical activity is beneficial, but in which patients and of what magnitude remains elusive, and statistical power provides only a glimpse of an answer.

Finally, the placebo effect remains a powerful, underestimated force in intervention studies of physical activity and other coronary risk factors for the prevention of cardiovascular disease and other outcomes. The commitment to participate in

an intervention study, particularly when it involves behavioral change, may be a greater determinant of increasing physical activity than the intervention itself. This is the quandary investigators face in the design of physical activity interventions; if treatment and follow-up are too short, the placebo effect may mask the intervention versus control effects; if treatment and follow-up are too long, recidivism may reduce the effects. For this reason, multiple assessments over the course of an intervention help to delineate these effects. The 1 to 3 mmHg reductions in systolic, diastolic, and pulse pressure along with 2 to 3 mg/dL increases in HDL-C observed by García-Ortiz et al¹ were modest, but may have been greater after accounting for the placebo effect and recidivism. The decreases in the atherogenic index and the D'Agostino scale attest to the possibility that seemingly disappointing results from a physical activity intervention can still result in modest improvements in cardiovascular risk profiles.

In designing intervention studies to increase physical activity levels, the potential rewards far outweigh the challenges. The Experimental Program for Physical Activity Promotion (PEPAF)¹³ represents an important step forward not only in our understanding of the effectiveness of increasing physical activity in the primary care setting, but also in showing how the observed increases in physical activity may translate to improvements in coronary risk factors.

REFERENCES

1. García-Ortiz L, Grandes G, Sánchez-Pérez A, Montoya I, Iglesias-Valiente JA, Recio Rodríguez JI, et al. Efecto en el riesgo cardiovascular de una intervención para la promoción del ejercicio físico en sujetos sedentarios por el médico de familia. *Rev Esp Cardiol*. 2010;63:1244-52.
2. Sesso HD, Paffenbarger RS, Jr, Lee IM. Physical activity and coronary heart disease risk in men: the Harvard Alumni Health Study. *Circulation*. 2000;102:975-80.
3. Sattelmair JR, Kurth T, Buring JE, Lee IM. Physical activity and risk of stroke in women. *Stroke*. 2010;41:1243-50.
4. Gill JM, Cooper AR. Physical activity and prevention of type 2 diabetes mellitus. *Sports Med*. 2008;38:807-24.
5. Chase NL, Sui X, Lee DC, Blair SN. The association of cardiorespiratory fitness and physical activity with incidence of hypertension in men. *Am J Hypertens*. 2009;22:417-24.
6. Lee IM, Djousse L, Sesso HD, Wang L, Buring JE. Physical activity and weight gain prevention. *JAMA*. 2010;303:1173-9.
7. Thompson PD, Franklin BA, Balady GJ, Blair SN, Corrado D, Estes NA, 3rd, et al. Exercise and acute cardiovascular events placing the risks into perspective: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism and the Council on Clinical Cardiology. *Circulation*. 2007;115:2358-68.
8. Shiroma EJ, Lee IM. Physical activity and cardiovascular health: lessons learned from epidemiological studies across age, gender, and race/ethnicity. *Circulation*. 2010;122:743-52.

9. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc.* 2007;39:1423-34.
10. Grandes G, Sanchez A, Sanchez-Pinilla RO, Torcal J, Montoya I, Lizarraga K, et al. Effectiveness of physical activity advice and prescription by physicians in routine primary care: a cluster randomized trial. *Arch Intern Med.* 2009;169:694-701.
11. Williams NH. "The wise, for cure, on exercise depend": physical activity interventions in primary care in Wales. *Br J Sports Med.* 2009;43:106-8.
12. Morgan O. Approaches to increase physical activity: reviewing the evidence for exercise-referral schemes. *Public Health.* 2005; 119:361-70.
13. Grandes G, Sánchez A, Torcal J, Ortega Sánchez-Pinilla R, Lizarraga K, Serra J; Grupo PEPAF. Protocolo para la evaluación multicéntrica del Programa Experimental de Promoción de la Actividad Física (PEPAF). *Aten Primaria.* 2003;32:475-80.